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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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09/551,405 04/17/00 MULLER R EPROV-15

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EXAMINER

MCKENZIE, T

ART UNIT

PAPER NUMBER

1624

DATE MAILED:

11/16/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.

09/551,405

Applicant(s)

MULLER ET AL.

Examiner

Thomas C McKenzie, Ph.D.

Art Unit

1624

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-8, 10-13, & 16-20 is/are pending in the application.
- 4a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 1-8, 10-13, & 16-20 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claims ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are objected to by the Examiner.
- 11) ☐ The proposed drawing correction filed on ____ is: a) ☐ approved b) ☐ disapproved.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

- 13) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. ____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

- 15) ☒ Notice of References Cited (PTO-892)
- 16) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) ____.
- 18) ☐ Interview Summary (PTO-413) Paper No(s). ____.
- 19) ☐ Notice of Informal Patent Application (PTO-152)
- 20) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to an application filed on 4/17/00. There are seventeen pending claims. Claims 1-7 are compound claims. Claims 8, 10-13, and 16-20 are process claims. The application concerns some crystal modifications of calcium N5-methyltetrahydrofolate and processes of preparing them.

Abstract

2. Applicant is reminded of the proper content of an abstract of the disclosure. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details. The abstract is too short and generic. Examiner suggests combining claims 4-7 and including the utility.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 12 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claim has the limitation "crystallization is

effected from a suspension.” A compound must be dissolved in order for it to be recrystallized. The term recrystallization has no meaning unless the compound being purified by such a process is able to dissolve in the solvent being used for the process. To quote Wiberg “Laboratory Technique in Organic Chemistry” “[r]ecrystallization involves dissolving a substance”. This is found in the first sentence in the paragraph labeled “Recrystallization” on page 99.

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 8 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase “from the resultant heated solution” is indefinite. Are applicants intending crystallization from a hot solution or crystallization at any temperature from a solution that has been heated above 60°C anytime during its history? If they are claiming recrystallization from a hot solution, then how hot must it be? Is 60°C during the crystallization intended or any temperature between 60°C and room temperature?

5. Claim 12 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase “the recrystallization is

effected from a suspension” is indefinite. This could mean that a one time the compound being recrystallized was in suspension in the solvent but eventually dissolved. If so, please see point #7. It could mean that the compound being recrystallized was never completely in solution. If so, please see point #3. It could mean that some impurity was never dissolved during the recrystallization process.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3 are rejected under 35 U.S.C. 102(b) as being anticipated by Scheib ('202). Applicants' three compound claims have the limitations of a calcium salt, the (6S) absolute configuration, and producing a calcium salt with more than three water molecules of crystallization. The reference teaches all of these in the first complete paragraph in column 2. Specifically in line 7 of column 2 "X5 H₂O".

7. Claims 8, and 10-14 are rejected under 35 U.S.C. 102(b) as being anticipated by Scheib ('202). Applicants' four process claims have the limitations of heating any salt in water to 85°C and affecting recrystallization. The reference teaches such processes in examples 2-4 in column 2. The N-ethyl-2-aminopyrrolidine salt

of N5-methyltetrahydrofolate is recrystallized from water at 85°C. The word “suspended” is used in line 23 of column 2, thus anticipating Applicants claim 12.

8. Claims 1-3 are rejected under 35 U.S.C. 102(b) as being anticipated by Muller ('655). Applicants' three compound claims have the limitations of a calcium salt, the (6S) absolute configuration, and producing a calcium salt with more than three water molecules of crystallization. The reference teaches all of these in lines 34-58 of column 7. Specifically Muller ('655) teaches in line 42 “the dihydrate” and in line 50 “pentahydrate”.

9. Claims 1 and 2 are rejected under 35 U.S.C. 102(b) as being anticipated by Marazza ('611). Applicants' two compound claims have the limitations of either the (6S) or the (6R) absolute configuration, and producing a salt with at least one water molecule of crystallization. The references teaches all of these in lines spanning 50 of column 9 to line 6 of column 11. The reference teaches the cyclohexylammonium salt and the elemental analysis reported in line 36 and 67 of column 10 makes clear this salt is a dihydrate.

10. Claims 1-3 are rejected under 35 U.S.C. 102(b) as being anticipated by Vecchi ('850). Applicants' three compound claims have the limitations of a calcium salt, the (6S) absolute configuration, and producing a calcium salt with more than three water molecules of crystallization. The reference teaches all of

these in lines 5-13 of column 4. The reference teaches a crystalline compound with a water content of 15.27%, which meets the limitation of more than three molecules of water of crystallization.

11. Claims 8, 10, 11, and 13, 16, and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Vecchi ('850). Applicants' six process claims have the limitations of heating a calcium salt in water to above 85°C and effecting recrystallization. The reference teaches such processes in line 5 of column 4 "[i]t can be recrystallized from boiling water". Water boils at 100°C, thus anticipating all of applicants claim limitations.

12. Claims 1 and 3 are rejected under 35 U.S.C. 102(b) as being anticipated by Gennari ('500). Applicants' two compound claims have the limitations of a calcium salt with more than three water molecules of crystallization and racemic N5-methyltetrahydrofolate. The reference teaches all of these in Example 7 in lines 1-28 of column 7. The reference teaches a "crystalline salt" in line 24 and "pentahydrate" in lines 26-27, which meets the limitation of applicants' claims.

13. Claim 5 is rejected under 35 U.S.C. 102(b) as being anticipated by Muller ('655). The Applicants have clearly demonstrated by power X-ray diffraction that they have characterized four different hydrates and crystal forms of calcium N5-methyltetrahydrofolate. In lines 26-29 of page 2 of the specification, Applicants

disclose that Type I is a trihydrate, Type II is a dihydrate, and Types III and IV are pentahydrates. Applicants' have demonstrated superior storage characteristics of one of these forms in the Table on page 5 of the specification. It is not clear, which of the four forms was used for this study. Applicants have also provided X-ray data on "amorphous" calcium N5-methyltetrahydrofolate in Figure 5. Claim 5 is drawn to a dihydrate crystalline salt. Muller ('655) teaches in line 42 of column 7, "the dihydrate".

14. Claims 6 and 7 are rejected under 35 U.S.C. 102(b) as being anticipated by Scheib ('202), Muller ('655), Vecchi ('850), or Gennari ('500). Applicants' two claims are drawn to two different pentahydrates. The four references all teach a pentahydrate as cited above. Applicants have not established that their Type III and Type IV crystalline forms are completely absent from the material taught by the four references. Both Muller ('655) and Vecchi ('850) refer to their salt as "crystalline", thus it is not clear the "amorphous" pentahydrate Applicants use for comparison purposes is the same as that taught by Muller ('655) or Vecchi ('850).

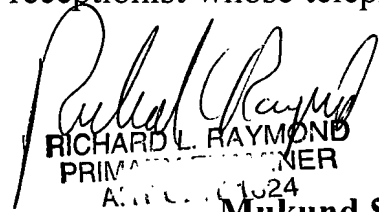
Allowable Subject Matter

15. Claims 4 and 18-20 are rejected as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. The following is a

statement of reasons for the indication of allowable subject matter: the prior art does not teach the trihydrate salt of Type I. Thus, the process of converting this salt into the other crystal forms must be novel as well.

Conclusion

16. Please direct any inquiry concerning this communication or earlier communications from the Examiner to Thomas C McKenzie, Ph. D. whose telephone number is (703) 308-9806. The Examiner is available from 8:30 to 5:30, Monday through Friday. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Mukund Shah can be reached on (703) 308-4716. The fax number for the organization where this application has been assigned is (703) 308-4556. Please direct any inquiry of a general nature or any inquiry relating to the status of this application to the receptionist whose telephone number is (703) 308-1235.


RICHARD L. RAYMOND
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Mukund Shah
Supervisory Patent Examiner
Art Unit 1624

TCMcK
November 8, 2000